Medtronic

MEDTRONIC PUERTO RICO OPERATIONS COMPANY

MPROC

STERILIZATION/LABORATORY QUALIFICATION/VALIDATION REPORT AND ROLL-UP DATA

Ethylene Oxide (EO) Dissipation Curve Testing Report for Ascenda ADT PFOA-Free PTFE Kit

Revision A

04SEP19

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1. HISTORY AND CONTROL SHEET

REVISION	DATE	DESCRIPTION
A	**04SEP19**	**New Release**

2. REPORT APPROVAL

Approval:

Giovanni R. Sánchez Cruz	See Agile MAP Signature
MPROC Juncos Microbiologist / Sterilization	Date
Brenda Simons	See Agile MAP Signature
Rice Creek Sr. Microbiologist	Date
Krystal Martinez Souchet	See Agile MAP Signature
Qual/Reg Affairs Contingent	Date

3. Validation Objectives / Purpose

The purpose of this report is to detail the results of the sterilant residual testing for the Ascenda ADT PFOA-Free PTFE Kit, hereinafter referred as "Ascenda ADT kit", listed in Table 1. Sterilant residual testing was performed, per plan D00064617, using dissipation curves to establish the minimum aeration time required to adequately reduce retained residuals to acceptable levels as per ISO 10993-7:2008/AC:2009 following 1X and 3X sterilization in the 100% EO 75-minute gas dwell Medtronic sterilization process.

4. Scope

The product model covered under the scope of this sterilization qualification is listed below in Table 1.

Table 1 – Product Model Information

Description	Model	Pin Number
Ascenda ADT PFOA-Free PTFE Kit	8781	878100001H

The following aspects of the Ascenda ADT kit sterilization are included in this report:

1. EO/ECH Residual
    a) Dissipation Curve
    b) Tolerable Contact Limit (TCL) Determination and/or Acute Irritation Testing (If necessary). Irritation test is only required if TCL results does not meet the requirements.

The following aspects of the Ascenda ADT kit sterilization validation and microbial testing are not included in this report:

1. Microbial Performance Qualification (MPQ)
2. Bioburden Estimation
3. Endotoxin Estimation
4. Physical Performance Qualification (PPQ) in the 3M 5XLe Steri-Vac™ 100% EO sterilizer and 3M XL/XLe aerator.

5. Background

Medtronic SynchroMed Pump is an implantable infusion system that stores and delivers medication according to instructions programmed by the physician. The Pump is used with the Ascenda catheter.

An Anchor Dispenser Tool (ADT) is required to implant the infusion system. The ADT places the anchor onto the Ascenda catheter. The anchor is then sutured in place to ensure the catheter is not dislodged from patient movement. An ADT hypotube's Polytetrafluoroethylene (PTFE) is current manufactured with low Perfluorooctanoic Acid (PFOA). However, since 2016, the Environmental Protection Agency (EPA) required PTFE to be applied without PFOA. Current estimate of last time to buy of ADTs with low PFOA PTFE stockouts is December 2019. This project is intended to qualify a PFOA free version of the hypotube to ensure this critical therapy component does not stock out .

New part numbers have been created for the Anchor Dispenser Tool (ADT) Assembly to reflect this change to the manufacturing process of the PTFE coating.

The Ascenda ADT kit will be sterilized using the 3M Model 5XLe Steri-Vac™ sterilizer within the 100% EO 75-minute gas dwell Medtronic sterilization process.

EO is the most common sterilizing agent used to sterilize medical devices, which are sensitive to heat or irradiation treatment. However, after the sterilization process, residual concentration of EO and Ethylene Chlorohydrin (ECH), might remain in the devices. These residues are potentially toxic, mutagenic, and carcinogenic substances. Therefore, it is required to remove them from the devices to avoid adverse effects in patients.

For reference, the Ascenda ADT kit is shown in its sterile package tray configuration in Figure 1 below.

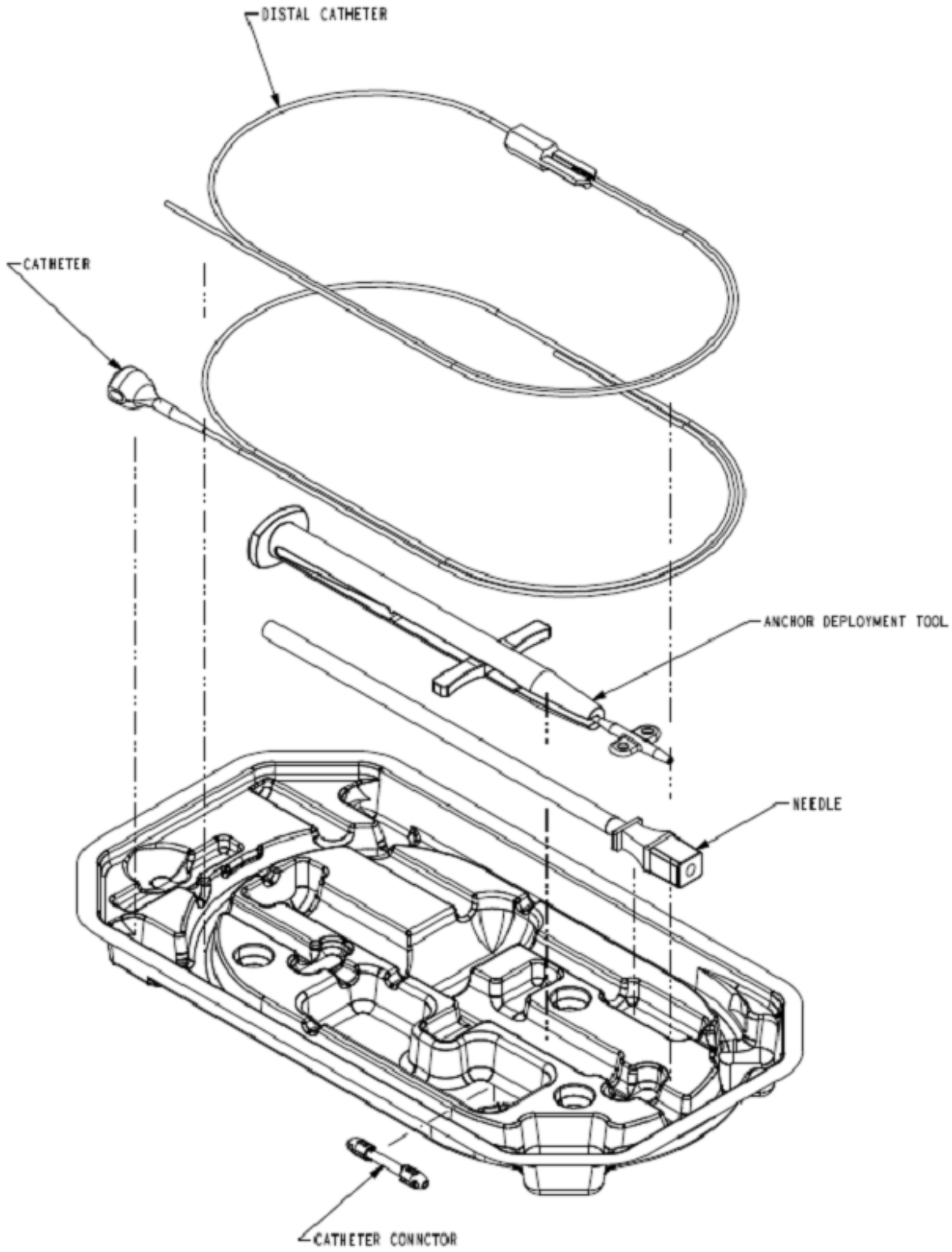

Figure 1. Ascenda ADT kit in Sterile Package

Table 2 – Kit Components and Patient Contact Relation

Component	Part Number	Body Contact Patient Contact
Distal Trident 26.0 in.	M970374A002	
Distal Trident 26.0 in.	M980676A002	Implant, (Tissue/bone) – Permanent
Trident Guidewire Assembly 26 in.	M980631A002	External Communicating (Tissue) - Limited
Catheter Proximal 29.0 in.	M970375A002	
Boot Connector	M980682A001	Implant, (Tissue/bone) – Permanent
Housing Connector	M980681A004	Implant, (Tissue/bone) – Permanent
Retaining Ring	M980683A001	Implant, (Tissue/bone) – Permanent
Molded Subassy Proximal Catheter 29 in.	M970460A001	Implant, (Tissue/bone) – Permanent
Guide Ring	M980680A002	Implant, (Tissue/bone) – Permanent
ROCC Assembly (Catheter connector)	M970376A001	Implant, (Tissue/bone) – Permanent
Anchor Dispenser Tool PTFE Coated	M978556A001	
ADT Base	M980926A001	External Communicating (Tissue) - Limited
ADT Handle	M978539A001	External Communicating (Tissue) - Limited
Bi-Wing Anchor	M980644A001	Implant, (Tissue) – Permanent
Needle Catheter Introducer 4.5 in.	M980672A002	External Communicating (Tissue) – Limited

Table 3 – Material Information of Components to be Tested

Component	Part Number	Material
Distal Trident 26.0 in.	M970374A002	
Distal Trident 26.0 in.	M980676A002	Resin-Polyether Urethane 55D, Polyether Urethane 80A, Silicone Tubing
Trident Guidewire Assembly 26 in.	M980631A002	PFOA-Free Guidewire Coating (Type L), Polypropylene
Catheter Proximal 29.0 in.	M970375A002	
Boot Connector	M980682A001	Rubber - Silicone
Housing Connector	M980681A004	Titanium
Retaining Ring	M980683A001	Molding-Nylon
Molded Subassy Proximal Catheter 29 in.	M970460A001	Silicone Rubber, Polyester Filament, Resin-Polyether Urethane – 80A, Resin-Polyether Urethane – 55
Guide Ring	M980680A002	Titanium
ROCC Assembly (Catheter connector)	M970376A001	Nylon Grilamid, Platinum, Iridium
Anchor Dispenser Tool PTFE Coated	M954321A001	
ADT Base	M980926A001	Polycarbonate
ADT Handle	M953012A001	Polycarbonate ,PTFE, Stainless Steel (SST-304)
Bi-Wing Anchor	M980644A001	Rubber - Silicone
Needle Catheter Introducer 4.5 in.	M980672A002	SST-304, Acrylic/Polycarbonate Alloy

Table 4 – Surface Area for Patient Surface Contact or Implantable Components

Component	Surface Area (cm^2)	Patient Contact
Bi-Wing Anchor	4.24	Permanent
Distal Trident 26.0 inch	51.34	Permanent
Catheter Proximal 29 inch (Pooled)	38.04	Permanent
ROCC Assembly	6.28	Permanent
Total Surface Area (cm^2)	**99.9**	

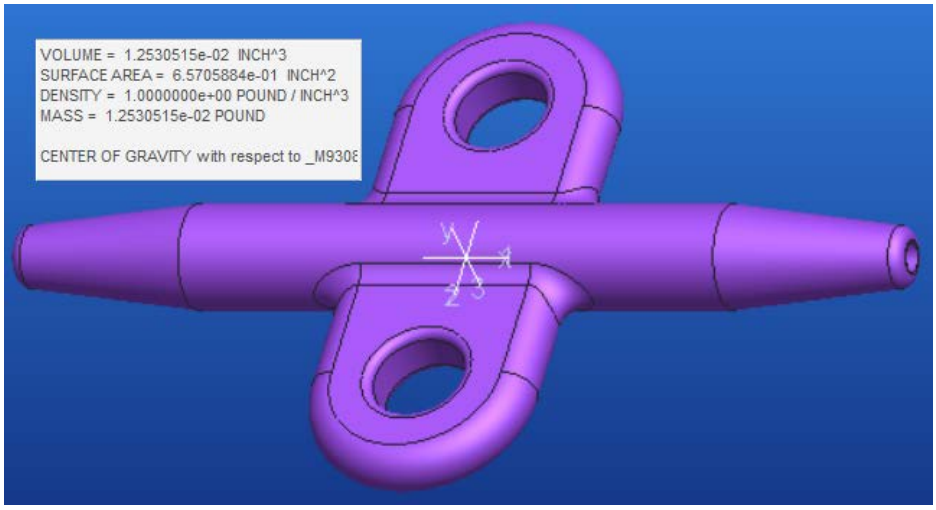

Figure 2 – Bi-Wing Anchor Surface Area (measurement in square inches)

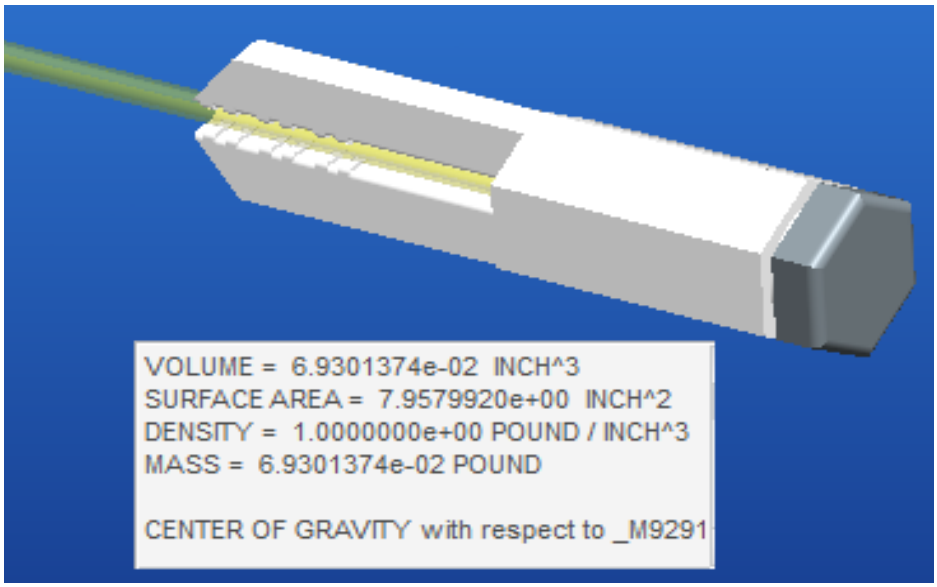

Figure 3 – Distal Trident 26.0in Surface Area (measurement in square inches)

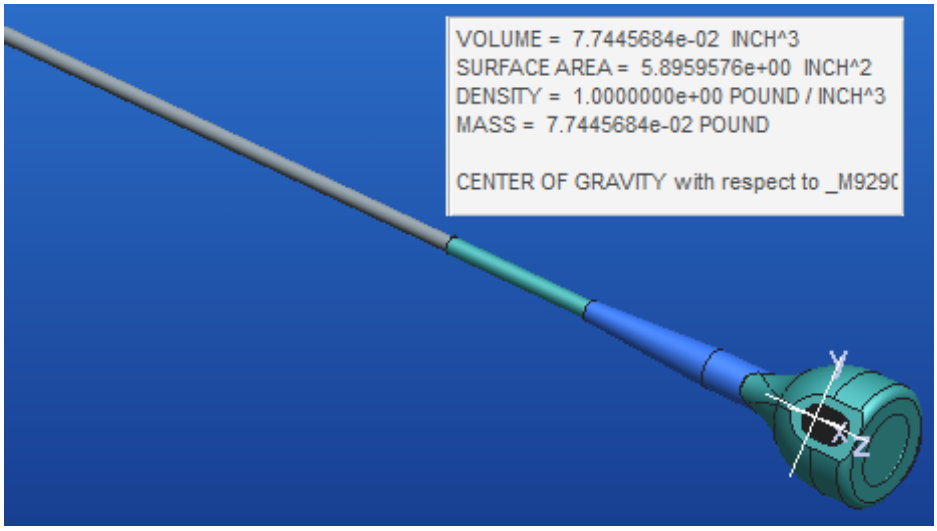

Figure 4 – Catheter Proximal 29-inch Surface Area (measurement in square inches)

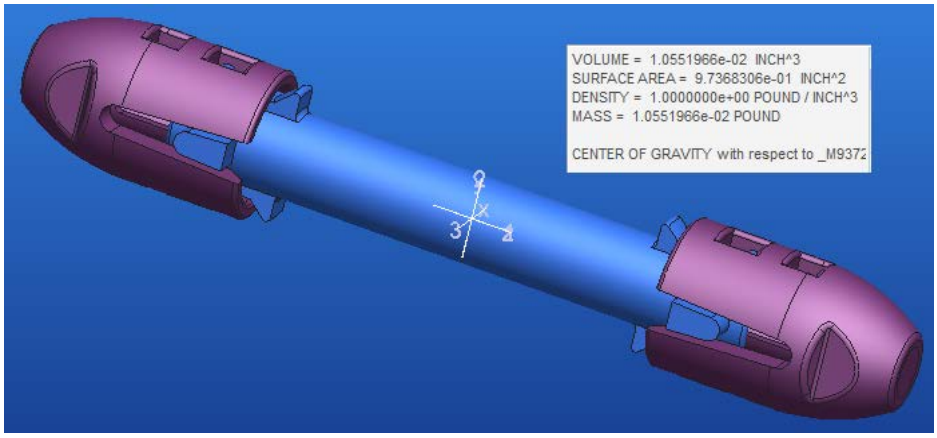

Figure 5 – ROCC Assembly Surface Area (measurement in square inches)

Sterilant Residuals:

Sterilant residual testing determines the minimum aeration time required to reduce EO and ECH residuals retained in a sterilized product, in order to meet the requirements of ISO 10993-7.

Tolerable Contact Limit (TCL):

ISO 10993-7:2008 added the TCL allowable limits (clause 4.3.5) to prevent acute localized tissue irritation resulting from EO or ECH released from the device off-gassing after terminal sterilization with EO. TCL was specifically intended to prevent local irritation by devices with low weight that have high concentrations of residuals.

6. Reference Documents

Table 5 – Reference Documents

Document Number	Document Title	Internal Repository
CRM-0902-0001	Ethylene Oxide Sterilization	Agile MAP
CSS-0401-0015	Sterilization Product Qualification and Maintenance	
1011299DOC	General Requirements for Sterilization Validation	
CSS-0501-XXXX-0007	Product Sterilization Qualification	
DOC000517	Development, Validation, and Requalification of the Product Aeration Process	
CSS-0901-0001-0008	Development, Validation, and Requalification of the 100% EO Sterilization Process	
CSS-0901-0001-0019	Ethylene Oxide Sterilizer System Equipment and Process Equivalence	
POD_000827	MPROC Neuromodulation Sterilization – 100% EtO	
D00064617	Ethylene Oxide (EO) Dissipation Curve Testing for Ascenda ADT PFOA-Free PTFE Kit	
200023	Medtronic Specification – Sterilization	Enovia
EN ISO 10993-7: 2008/ AC: 2009	Biological Evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals	External standard / Guidance
ISO 10993-10:2010	Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization	
EN ISO 11135: 2014	Sterilization of health-care products – Ethylene Oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices	
EN 556-1: 2001 / AC: 2006	Sterilization of medical devices – Requirements for Medical Devices to be designated “Sterile” Part 1: Requirements for terminally sterilized medical devices	
AAMI TIR 28: 2009	Product adoption and process equivalency for ethylene oxide sterilization	

7. Validation / Qualification Results

A. Definitions

Table 6 – Abbreviations, Acronyms, and Definitions

Term	Term Description
%RH	Relative humidity percentage
AAMI	Association for the Advancement of Medical Instrumentation
ADD	Average Daily Dose
ANSI	American National Standards Institute
CDA	Complete Device Assembly
CI	Confidence Interval
EO	Ethylene Oxide
ECH	Ethylene Chlorohydrin
EN	European Standard (Europäische Norm)
ISO	International Organization for Standardization
MPROC	Medtronic Puerto Rico Operations Center
PFOA	Perfluorooctanoic Acid
PTFE	Polytetrafluoroethylene
TCL	Tolerable Contact Limit

B. Equipment

The sterilization equipment used is listed in Table 7. Calibration records are stored in SAP.

Table 7 – Equipment / Fixturing and Gauging

Description	Identification Number	Calibration Due Date
3M 5XLe Steri-Vac™ sterilizer - The 5XLe system is described as a self-contained, table-top, ethylene oxide sterilizer with internal volume equaling 136 liters/0.136 m^3 (4.8 ft^3) and does not rely on any ancillary equipment to provide heat, steam, or vacuum functions. The internal chamber is made of brushed aluminum with one front mounted door.	5XLe-10 / MR100-718	25OCT19
3M XLe Aerator - The XLe aerator is described as a self-contained, table-top aerator with internal volume equaling 150 liters/0.15 m^3 (5.3 ft^3) and does not rely on any ancillary equipment to provide heat. The internal chamber is made of brushed aluminum with one front mounted door.	XLe-47 / 54210-635	29NOV19

Note- All sterilizer systems (sterilizer and aerator) in MPROC Juncos are maintained as equivalent per CSS-0901-0001-0019 - Ethylene Oxide Sterilizer System Equipment and Process Equivalence. Equipment equivalence is established and documented by identical chamber modification, IQ activities, maintenance and calibration performed on all sterilizers and aeration chambers in the facility. This ensures that all sterilizers and aerators are configured identically and that validated sterilization and aeration processes are performed in an equivalent manner at each manufacturing facility.

C. Materials Used

The materials that used for testing are listed in Table 8 below. Test materials used by the testing laboratory are documented through applicable laboratory procedure(s).

Table 8 – Materials

Description	Part Number	Lot Number	Expiration Date
3M 4-134 EO gas cartridge	168651001	0009678752	31MAY23
		0009741486	31MAY23
Ascenda ADT Kit – Dissipation Curve	878100001H	19 units (3 samples per 3 sterilization lots for both 1X and 3X, plus 1 control sample/blank)	
Laboratory Testing Supplies	As documented in applicable laboratory test procedure	As required per applicable laboratory test procedure	

D. Software Identification

Sterilization software used is listed in Table 9. Software used by Chemical Technologies in EO residual testing is on file at Chemical Technologies Department. Software used by Metrology is on file at Metrology Department.

Table 9 – Software

Software Name	Revision
Eurotherm Review	4.1.323
StAR System	1.0.6

E. Training Assessment and Responsibilities

1. Rice Creek and MPROC Juncos Sterilization Specialist/Microbiologist:
   a) Responsible for developing protocol and report, conduct and/or oversee testing and evaluate test results.
2. MPROC Juncos Quality engineer:
   a) Responsible of reviewing the protocol, report and the data obtained during qualification.
3. Medtronic Manufacturing:
   a) Build test samples per appropriate procedures.
4. Calibration / Metrology Tech
   a) Responsible for EO sterilizer and aerator profiling and calibration per appropriate procedures.
5. Pace Analytical Laboratory, or other approved EO/ECH residual testing laboratory
   a) Responsible for conducting residual testing of product.

F. Sample Size Strategy

Load Configuration

The "S" load configuration consists of:

- Forty-eight (48) catheter trays will be placed at the Top Sterilizer Wire rack. Forty-two (42) catheter trays will be placed at the Bottom Sterilizer Wire rack.
    - Six (6) stacks of catheter trays are in each basket.
    - Each stack in the Top Sterilizer Wire rack has eight (8) catheter trays as specified in the figure above.
    - Each stack in the Bottom Sterilizer Wire rack has seven (7) catheter trays as specified in the figure above.
    - The Tyvek side of the package is up.

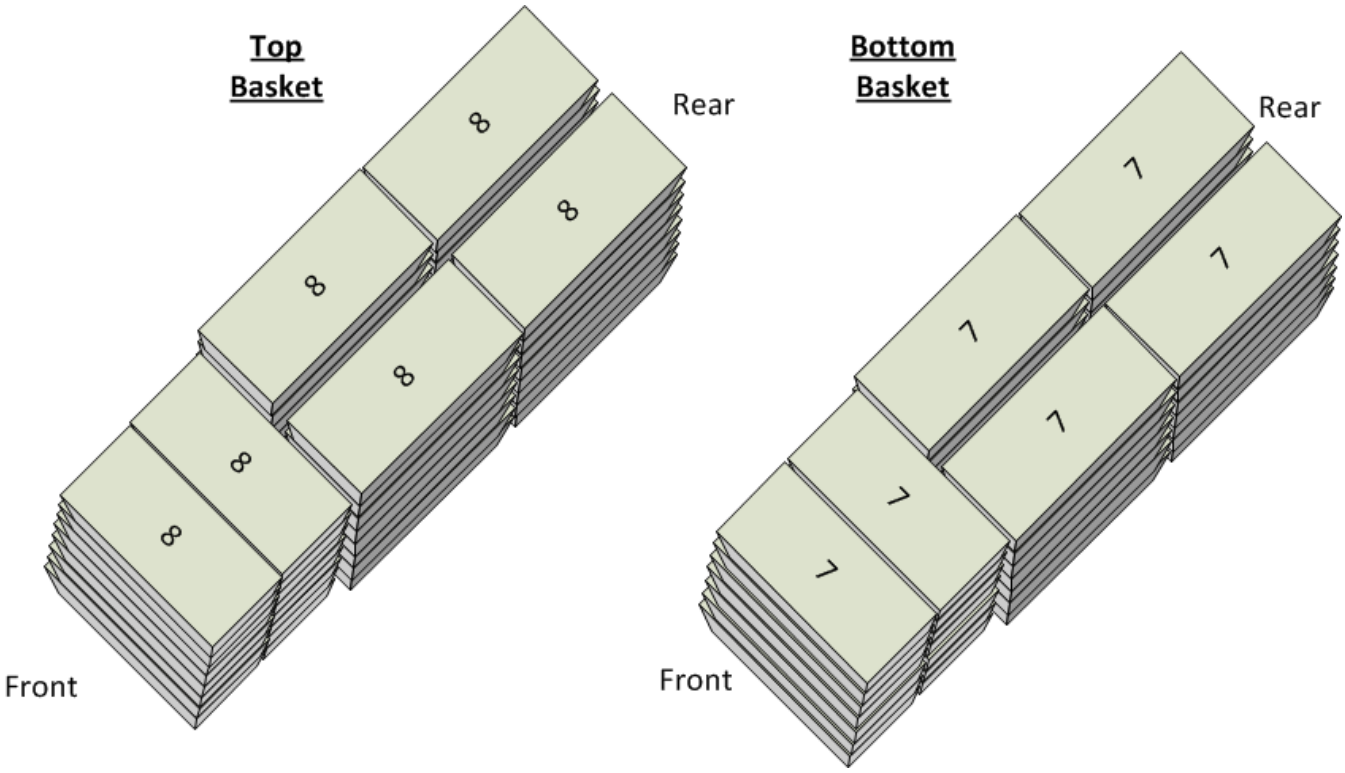

Figure 3 – Configuration "S"

Table 10 - Ascenda ADT Kit Sample Utilization

Samples Needed	Rationale for Quantity of Samples Required
19	• One (1) sample following 0X sterilization which was reserved as a non-sterilized, manufactured control sample. • Nine (9) samples following 1X sterilization for EO/ECH residuals test per Table 11. • Nine (9) samples following 3X sterilization for EO/ECH residuals test per Table 11.

G. Sampling Strategy

Sterilant Residual and TCL Testing

The approach chosen for qualifying the sterilant residuals of Ascenda ADT kit was the dissipation curve method. Sterilant residual dissipation curves are constructed from a minimum of three samples per three sterilization lots run at different aeration times to establish the minimum required aeration time. Required aeration time was determined following 1X and 3X sterilization exposures in the 100% EO 75-minute gas dwell Medtronic sterilization process. Samples were tested following 1hrs, 6hrs and 12hrs aeration. Residual test sample types and quantities are detailed in Table 11 below.

Table 11 – Sample Quantities and Sterilization Cycle Requirements

# of Sterilization Exposures	Test Type	Quantity of Test Samples	Rationale for Test Sample Quantity
0X	Residual	1	(1) EO/ECH Control Sample (“Unexposed Blank”) – 0X
1X	Residual	9	(1) sample each for 1hrs, 6hrs and 12hrs from three different sterilization lots
3X	Residual	9	(1) sample each for 1hrs, 6hrs and 12hrs from three different sterilization lot combinations

Test samples were built using materials, designs, packaging, and manufacturing processes that mimic the final, finished product intended to be sold. Samples were labeled to designate sample set 1, 2 or 3, sterilization cycle, aeration time and type of testing (i.e. residual or irritation). EO/ECH control sample was labeled accordingly. Refer to Table 13.

Dissipation Curve Sample Set:

- Sample kits for test were prepared using Figures 1 and Table 12.
- The entire load was subjected to 75-minutes 100% EO sterilization cycle at MPROC Juncos per POD_000827.
- Immediately following completion of the sterilization cycle, the load was placed into a forced heat aerator (see Table 12 for aeration times). The forced heat aeration timing begins immediately upon placement of samples within the aerator at ambient temperature. The aerator takes 20 to 30 minutes to reach the required temperature set point and simulates “worst-case” conditions for residual dissipation from the product.
- The designated samples were removed and replaced with a dummy at each of the following intervals:
  - Following 1hrs aeration, the #X-a (1hrs) samples were removed.
  - Following 6hrs aeration, the #X-b (6hrs) samples were removed.
  - Following 12hrs aeration, the #X-c (12hrs) samples were removed.
- All samples were frozen until completion of all sterilization cycles and then all samples were shipped on dry ice to Pace Analytical external laboratory for testing.

These instructions were repeated for all three runs.

Table 12 – Sample Distribution per Cycle / Testing Timeline

*Note: On Table 12, the number before the X refers to the number of sterilizations, the number before letter (a, b or c) refers sample set and letter refer to designated aeration time (a = 1hr, b = 6 hours and c = 12 hours)

Samples	Day/Run 1	Day/Run 2	Day/Run 3	Day/Run 4	Day/Run 5
1 Hours Aeration Time	(1) 1X-1a (1) 3X-1a	(1) 1X-2a (1) 3X-1a (1) 3X-2a	(1) 1X-3a (1) 3X-1a (1) 3X-2a (1) 3X-3a	(1) 3X-2a (1) 3X-3a	(1) 3X-3a
6 Hours Aeration Time	(1) 1X-1b (1) 3X-1b	(1) 1X-2b (1) 3X-1b (1) 3X-2b	(1) 1X-3b (1) 3X-1b (1) 3X-2b (1) 3X-3b	(1) 3X-2b (1) 3X-3b	(1) 3X-3b
12 Hours Aeration Time	(1) 1X-1c (1) 3X-1c	(1) 1X-2c (1) 3X-1c (1) 3X-2c	(1) 1X-3c (1) 3X-1c (1) 3X-2c (1) 3X-3c	(1) 3X-2c (1) 3X-3c	(1) 3X-3c
Total number of samples in the run	**6**	**9**	**12**	**6**	**3**

Irritation testing was not required based on residual results meeting TCL requirements. Additional sterilization runs, and additional irritation test samples were not required.

Residual Testing (Total EO and ECH)

The samples were analyzed to evaluate EO and ECH by gas chromatography utilizing the water extraction method. Testing methodology was conducted in compliance with EN ISO 10993-7:2008.

Components were grouped based on exposure categories, Limited or Implant/Permanent and were pooled for testing.

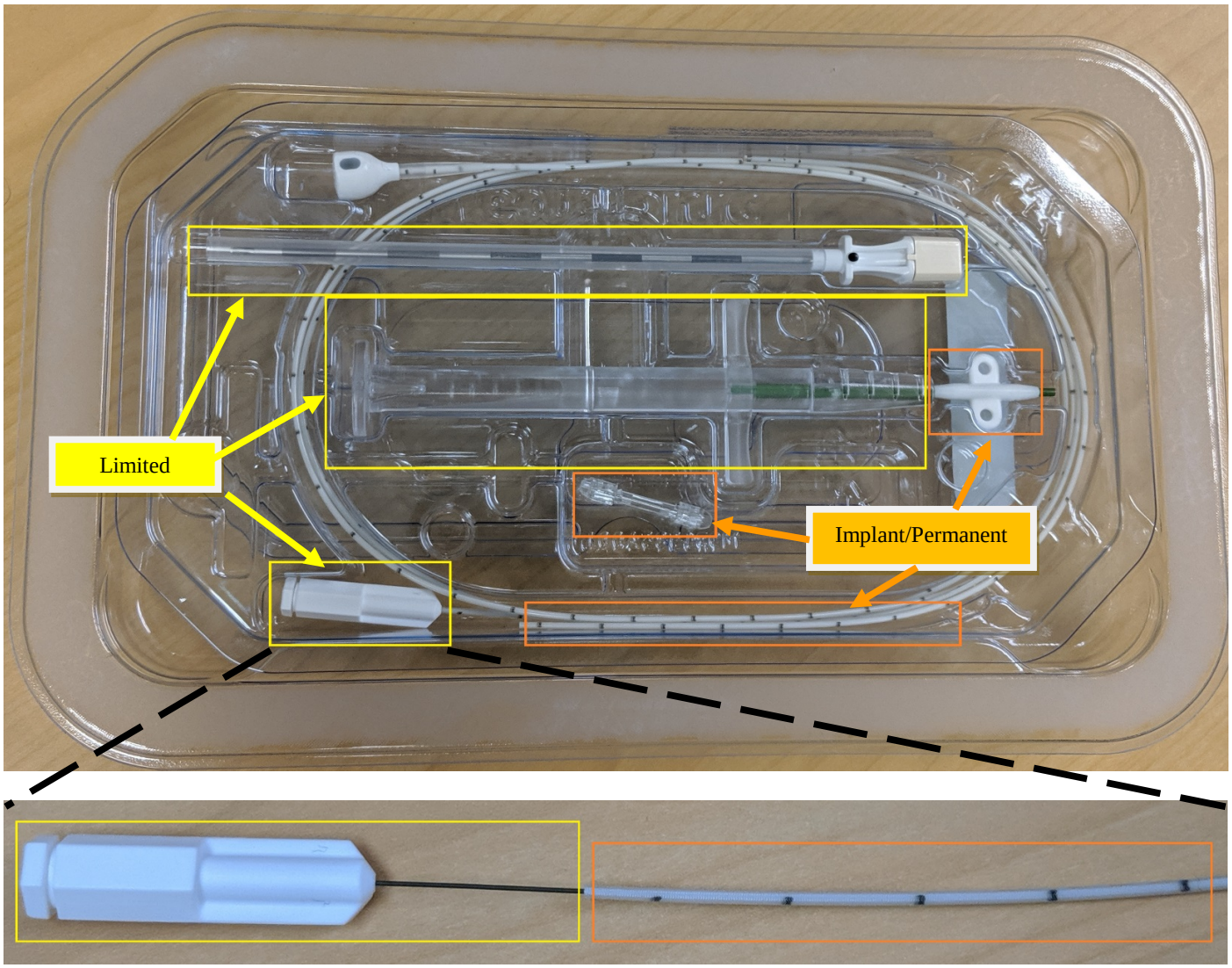

Figure 4. Component division for testing

Table 13 – Extraction conditions

Component	Part Number	Body Contact Patient Contact	Extraction Conditions
Distal Trident 26.0 in.	M970374A002		
Distal Trident 26.0 in.	M980676A002	Implant, (Tissue/bone) – Permanent	Exhaustive
Trident Guidewire Assembly 26 in.	M980631A002	External Communicating (Tissue) - Limited	Simulated Use extraction for 1 hours at 37ºC
Catheter Proximal 29.0 in.	M970375A002		
Boot Connector	M980682A001	Implant, (Tissue/bone) – Permanent	Exhaustive
Housing Connector	M980681A004	Implant, (Tissue/bone) – Permanent	Exhaustive
Retaining Ring	M980683A001	Implant, (Tissue/bone) – Permanent	Exhaustive
Molded Subassy Proximal Catheter 29 in.	M970460A001	Implant, (Tissue/bone) – Permanent	Exhaustive
Guide Ring	M980680A002	Implant, (Tissue/bone) – Permanent	Exhaustive
ROCC Assembly (Catheter connector)	M970376A001	Implant, (Tissue/bone) – Permanent	Exhaustive
Anchor Dispenser Tool PTFE Coated	M954321A001		
ADT Base	M980926A001	External Communicating (Tissue) - Limited	Simulated Use extraction for 1 hours at 37ºC
ADT Handle	M953012A001	External Communicating (Tissue) - Limited	Simulated Use extraction for 1 hours at 37ºC
Bi-Wing Anchor	M980644A001	Implant, (Tissue) – Permanent	Exhaustive
Needle Catheter Introducer 4.5 in.	M980672A002	External Communicating (Tissue) – Limited	Simulated Use extraction for 1 hours at 37ºC

H. Acceptance Criteria

Sterilant Residual and TCL Testing

Acceptance Criteria

The upper 95% CI of the mean sterilant residual levels as well as the Tolerable Contact Limit (TCL) obtained from the test model samples must be below the levels stated in Table 14 thru Table 16. These requirements must be met following a single or multiple exposure(s) to an EO sterilization process.

Table 14 – Sterilant Residual Requirements

Permanent Exposure Acceptance Criteria:	**Total EO:**	**Total ECH:**
Dose for first 24 hours not to exceed	4 mg	9 mg
Dose for first 30 days not to exceed	60 mg	60 mg
Dose for lifetime not to exceed	2.5 g	10 g
TCL (Or show negligible irritation per ISO 10993-10)	10 µg / cm^2	5 mg / cm^2
Average Daily Dose	0.1 mg/day	0.4 mg/day
Limited Exposure Acceptance Criteria	**Total EO:**	**Total ECH:**
Dose for first 24 hours not to exceed	4 mg	9 mg
TCL (Or show negligible irritation per ISO 10993-10)	10 µg / cm^2	5 mg / cm^2
Average Daily Dose	4 mg/day	9 mg/day

Permanent contact products have the requirement that the average daily dose ($\mathbf{M_{add}}$ or ADD) of EO to patient shall not exceed 0.1 mg per day. This is calculated using the formulas found in clause 4.4.7.2 of ISO 10993-7:

Permanent Contact: $M_{add} = M_d / 25{,}000$
Prolonged Exposure: $M_{add} = M_d / 30$
Limited Exposure: $M_{add} = M_d$

M_d – extract residue in milligrams
25,000 – number of days per lifetime
30 – number of days per month

Table 15 demonstrates that if you meet the 24-hour, 30 day and lifetime requirements that you will automatically meet the average daily dose requirements as the average daily dose limit is derived from dividing the exposure limit by the number of days in the exposure group i.e. 30 days for prolonged exposure.

Note that pediatric limits lower than those in ISO 10993-7:2008 are not applied to these devices. Per Medtronic document MDT30068705, the adult patient population accounts for the dominant use of Neuromodulation products. Due to the low pediatric use, compliance with ISO 10993-7:2008, and the absence of published reports regarding adverse effects associated with EO residuals, Medtronic believes that the risks of EO residuals in pediatric patients are outweighed by the benefits the implants provide. Therefore, it is unnecessary to adjust allowable limits of EO for pediatric or neonatal subpopulations.

Table 15 – Demonstration that ADD limits are met when 24hour, 30 day and lifetime requirements are met

Exposure Acceptance Criteria	Total EO	Total ECH	Average Daily Dose EO	Average Daily Dose ECH
Limited Exposure *Dose for first 24 hours not to exceed*	4 mg	9 mg	4 mg	9 mg
Prolonged Exposure *Dose for first 30 days not to exceed*	60 mg	60 mg	60 mg / 30 days = 2 mg	60 mg / 30 days = 2 mg
Permanent Contact *Dose for lifetime not to exceed*	2.5 g	10 g	2,500 mg / 25,000 days = 0.1 mg	10,000 mg / 25,000 days = 0.4 mg

Per ISO 10993-7:2008 Annex G.8.5 Limit based on TCL value
For surface-contacting devices, a TCL-based limit is relevant. The formula for calculation of a mass limit based on the TCL is as follows:

$$m\text{dev, BSC} = \text{TCL} \times A$$

where,
*m*dev, BSC is the allowable residual mass per device, i.e. maximum dose to patient, in milligrams;
TCL is the tolerable contact limit, in milligrams per square centimeter;
A is the surface area of medical device in contact with the body, in square centimeters.

Therefore, for individual devices, the approximate area in square centimeters would be multiplied by the TCL of 10 µg/cm^2 to arrive at the device limit.

EXAMPLE Device surface area in contact with the body = 100 cm^2:

$$m\text{dev, BSC} = 10\ \mu g/cm^2 \times 100\ cm^2 => 1000\ \mu g => 1\ mg$$

Table 16 - TCL Limits for model B31060

Component	Surface Area (cm^2)	TCL limit (mg)
Bi-Wing Anchor	4.24	
Distal Trident 26.0 inch	51.34	
Catheter Proximal 29 inch (Pooled)	38.04	
ROCC Assembly	6.28	
Total Surface Area (cm^2)	**99.9**	**EO – 0.999** **ECH – 499.5**

Test Results
Test sample and sterilization information is listed in Table 17. Test results for the unexposed "blank" is summarized in Table 18. Test results for 1X and 3X samples are summarized in Table 19 to Table 30.

Table 17 – Sterilant Residual Test Sample and Sterilization Information

Pace Work Order	Sterile Lot / Run Number	Sterilization Date	Sample Identification / Test Type (Pace ID)
9074016– 1X 9074017 – 3X	N/A	N/A	Control
	D00064617 / Run 1	23JUL19	1X-1a EO/ECH 1X-1b EO/ECH 1X-1c EO/ECH 3X-1a EO/ECH 3X-1b EO/ECH 3X-1c EO/ECH
	D00064617 / Run 2	31JUL19	1X-2a EO/ECH 1X-2b EO/ECH 1X-2c EO/ECH 3X-1a EO/ECH 3X-1b EO/ECH 3X-1c EO/ECH 3X-2a EO/ECH 3X-2b EO/ECH 3X-2c EO/ECH
	D00064617 / Run 3	01AUG19	1X-3a EO/ECH 1X-3b EO/ECH 1X-3c EO/ECH 3X-1a EO/ECH 3X-1b EO/ECH 3X-1c EO/ECH 3X-2a EO/ECH 3X-2b EO/ECH 3X-2c EO/ECH 3X-3a EO/ECH 3X-3b EO/ECH 3X-3c EO/ECH
	D00064617 / Run 4	05AUG19	3X-2a EO/ECH 3X-2b EO/ECH 3X-2c EO/ECH 3X-3a EO/ECH 3X-3b EO/ECH 3X-3c EO/ECH
	D00064617 / Run 5	06AUG19	3X-3a EO/ECH 3X-3b EO/ECH 3X-3c EO/ECH

Table 18 – Sterilant Residual Extraction Information and Results for 0X

Device Requirement Description	Acceptance Criteria		Components Extracted	Extraction Method	Extraction Condition	EO	ECH
	EO	ECH					
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Limited Contact Components Pooled**	**Simulated**	**37°C**	Not Detected	
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Exhaustive Contact Components Pooled**	**Exhaustive**	**37°C**	Not Detected	
Dose for first 30 days not to exceed	**60 mg**	**60 mg**					
Dose for lifetime not to exceed	**2.5 g**	**10 g**					
Average Daily Dose ***Dose not to exceed for lifetime***	**0.1 mg / day**	**0.4 mg / day**					
Pass or Fail						**Pass**	

Table 19 – Sterilant Residual Extraction Information and Results for 1X / 1-hour aeration

Device Requirement Description	Acceptance Criteria		Components Extracted	Extraction Method	Extraction Condition	1X-1a / 1hrs aeration Results (mg)		1X-2a / 1hrs aeration Results (mg)		1X-3a / 1hrs aeration Results (mg)	
	EO	ECH				EO	ECH	EO	ECH	EO	ECH
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Limited Contact Components Pooled**	**Simulated**	**37°C**	0.4223	N/D*	0.4842	N/D*	0.4087	N/D*
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Exhaustive Contact Components Pooled**	**Exhaustive**	**37°C**	1.2441	N/D*	1.2419	N/D*	1.0905	N/D*
Dose for first 30 days not to exceed	**60 mg**	**60 mg**				1.4063	N/D*	1.4007	N/D*	1.2308	N/D*
Dose for lifetime not to exceed	**2.5 g**	**10 g**				1.4063	N/D*	1.4007	N/D*	1.2308	N/D*
Average Daily Dose ***Dose not to exceed for lifetime***	**0.1 mg / day**	**0.4 mg / day**				5.6252 E-05	N/D*	5.6028 E-05	N/D*	4.9232 E-05	N/D*
Pass or Fail						**Pass**	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**

*N/D = Not detected

Table 20 – Sterilant Residual Extraction Information and Results for 1X / 6-hour aeration

Device Requirement Description	Acceptance Criteria		Components Extracted	Extraction Method	Extraction Condition	1X-1b / 6hrs aeration Results (mg)		1X-2b / 6hrs aeration Results (mg)		1X-3b / 6hrs aeration Results (mg)	
	EO	ECH				EO	ECH	EO	ECH	EO	ECH
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Limited Contact Components Pooled**	**Simulated**	**37°C**	0.0774	N/D*	0.0900	N/D*	0.1688	N/D*
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Exhaustive Contact Components Pooled**	**Exhaustive**	**37°C**	0.3592	N/D*	0.3512	N/D*	0.3455	N/D*
Dose for first 30 days not to exceed	**60 mg**	**60 mg**				0.4374	N/D*	0.4252	N/D*	0.4197	N/D*
Dose for lifetime not to exceed	**2.5 g**	**10 g**				0.4374	N/D*	0.4252	N/D*	0.4197	N/D*
Average Daily Dose ***Dose not to exceed for lifetime***	**0.1 mg / day**	**0.4 mg / day**				1.7496 E-05	N/D*	1.7008 E-05	N/D*	1.6788 E-05	N/D*
Pass or Fail						**Pass**	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**

*N/D = Not detected

Table 21 – Sterilant Residual Extraction Information and Results for 1X / 12-hour aeration

Device Requirement Description	Acceptance Criteria		Components Extracted	Extraction Method	Extraction Condition	1X-1c / 12hrs aeration Results (mg)		1X-2c / 12hrs aeration Results (mg)		1X-3c / 12hrs aeration Results (mg)	
	EO	ECH				EO	ECH	EO	ECH	EO	ECH
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Limited Contact Components Pooled**	**Simulated**	**37°C**	0.0448	N/D*	0.0583	N/D*	0.1068	N/D*
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Exhaustive Contact Components Pooled**	**Exhaustive**	**37°C**	0.2116	N/D*	0.2070	N/D*	0.1931	N/D*
Dose for first 30 days not to exceed	**60 mg**	**60 mg**				0.2583	N/D*	0.2523	N/D*	0.2405	N/D*
Dose for lifetime not to exceed	**2.5 g**	**10 g**				0.2583	N/D*	0.2523	N/D*	0.2405	N/D*
Average Daily Dose ***Dose not to exceed for lifetime***	**0.1 mg / day**	**0.4 mg / day**				1.0332 E-05	N/D*	1.0092 E-05	N/D*	9.6200 E-06	N/D*
Pass or Fail						**Pass**	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**

*N/D = Not detected

Table 22 – Sterilant Residual Extraction Information and Results for 3X / 1-hour aeration

Device Requirement Description	Acceptance Criteria		Components Extracted	Extraction Method	Extraction Condition	3X-1a / 1hrs aeration Results (mg)		3X-2a / 1hrs aeration Results (mg)		3X-3a / 1hrs aeration Results (mg)	
	EO	ECH				EO	ECH	EO	ECH	EO	ECH
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Limited Contact Components Pooled**	**Simulated**	**37°C**	0.6660	N/D*	0.7312	N/D*	0.7153	N/D*
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Exhaustive Contact Components Pooled**	**Exhaustive**	**37°C**	1.3642	N/D*	1.5117	N/D*	1.5696	N/D*
Dose for first 30 days not to exceed	**60 mg**	**60 mg**				1.6208	N/D*	1.7713	N/D*	1.8312	N/D*
Dose for lifetime not to exceed	**2.5 g**	**10 g**				1.6208	N/D*	1.7713	N/D*	1.8312	N/D*
Average Daily Dose ***Dose not to exceed for lifetime***	**0.1 mg / day**	**0.4 mg / day**				6.4832 E-05	N/D*	7.0852 E-05	N/D*	7.3248 E-05	N/D*
Pass or Fail						**Pass**	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**

*N/D = Not detected

Table 23 – Sterilant Residual Extraction Information and Results for 3X / 6-hour aeration

Device Requirement Description	Acceptance Criteria		Components Extracted	Extraction Method	Extraction Condition	3X-1b / 6hrs aeration Results (mg)		3X-2b / 6hrs aeration Results (mg)		3X-3b / 6hrs aeration Results (mg)	
	EO	ECH				EO	ECH	EO	ECH	EO	ECH
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Limited Contact Components Pooled**	**Simulated**	**37°C**	0.2583	N/D*	0.2372	N/D*	0.2968	N/D*
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Exhaustive Contact Components Pooled**	**Exhaustive**	**37°C**	0.4987	N/D*	0.4722	N/D*	0.4493	N/D*
Dose for first 30 days not to exceed	**60 mg**	**60 mg**				0.6405	N/D*	0.6077	N/D*	0.5800	N/D*
Dose for lifetime not to exceed	**2.5 g**	**10 g**				0.6405	N/D*	0.6077	N/D*	0.5800	N/D*
Average Daily Dose ***Dose not to exceed for lifetime***	**0.1 mg / day**	**0.4 mg / day**				2.5620 E-05	N/D*	2.4308 E-05	N/D*	2.3200 E-05	N/D*
Pass or Fail						**Pass**	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**

*N/D = Not detected

Table 24 – Sterilant Residual Extraction Information and Results for 3X / 12-hour aeration

Device Requirement Description	Acceptance Criteria		Components Extracted	Extraction Method	Extraction Condition	3X-1c / 12hrs aeration Results (mg)		3X-2c / 12hrs aeration Results (mg)		3X-3c / 12hrs aeration Results (mg)	
	EO	ECH				EO	ECH	EO	ECH	EO	ECH
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Limited Contact Components Pooled**	**Simulated**	**37°C**	0.1621	N/D*	0.1926	N/D*	0.2188	N/D*
Dose for first 24 hours not to exceed	**4 mg**	**9 mg**	**Exhaustive Contact Components Pooled**	**Exhaustive**	**37°C**	0.2919	N/D*	0.2987	N/D*	0.2480	N/D*
Dose for first 30 days not to exceed	**60 mg**	**60 mg**				0.3782	N/D*	0.3807	N/D*	0.3288	N/D*
Dose for lifetime not to exceed	**2.5 g**	**10 g**				0.3782	N/D*	0.3807	N/D*	0.3288	N/D*
Average Daily Dose ***Dose not to exceed for lifetime***	**0.1 mg / day**	**0.4 mg / day**				1.5128 E-05	N/D*	1.5228 E-05	N/D*	1.3152 E-05	N/D*
Pass or Fail						**Pass**	**Pass**	**Pass**	**Pass**	**Pass**	**Pass**

*N/D = Not detected

Table 25 – EO TCL Results for 1X / 1-hour aeration for Exhaustive Contact Components Pooled

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	1X-1a / 1hrs aeration Results (mg)	1X-2a / 1hrs aeration Results (mg)	1X-3a / 1hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	1X, 1-hour heated aeration	99.9	0.999	1.2441	1.2419	1.0905
ECH	Not to exceed 5 mg/cm^2			499.5	N/D*	N/D*	N/D*

*N/D = Not detected

Table 26 – EO TCL Results for 1X / 6-hour aeration for Exhaustive Contact Components Pooled

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	1X-1b / 6hrs aeration Results (mg)	1X-2b / 6hrs aeration Results (mg)	1X-3b / 6hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	1X, 6-hour heated aeration	99.9	0.999	0.3592	0.3512	0.3455
ECH	Not to exceed 5 mg/cm^2			499.5	N/D*	N/D*	N/D*

*N/D = Not detected

Table 27 – EO TCL Results for 1X / 12-hour aeration for Exhaustive Contact Components Pooled

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	1X-1c / 12hrs aeration Results (mg)	1X-2c / 12hrs aeration Results (mg)	1X-3c / 12hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	1X, 12-hour heated aeration	99.9	0.999	0.2116	0.2070	0.1931
ECH	Not to exceed 5 mg/cm^2			499.5	N/D*	N/D*	N/D*

*N/D = Not detected

Table 28 – EO TCL Results for 3X / 1-hour aeration for Exhaustive Contact Components Pooled

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	3X-1a / 1hrs aeration Results (mg)	3X-2a / 1hrs aeration Results (mg)	3X-3a / 1hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	3X, 1-hour heated aeration	99.9	0.999	1.3642	1.5117	1.5696
ECH	Not to exceed 5 mg/cm^2			499.5	N/D*	N/D*	N/D*

*N/D = Not detected

Table 29 – EO TCL Results for 3X / 6-hour aeration for Exhaustive Contact Components Pooled

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	3X-1b / 6hrs aeration Results (mg)	3X-2b / 6hrs aeration Results (mg)	3X-3b / 6hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	3X, 6-hour heated aeration	99.9	0.999	0.4987	0.4722	0.4493
ECH	Not to exceed 5 mg/cm^2			499.5	N/D*	N/D*	N/D*

*N/D = Not detected

Table 30 – EO TCL Results for 3X / 12-hour aeration for Exhaustive Contact Components Pooled

Residual	TCL Acceptance Criteria	Extraction Set	A (cm^2)	$m_{dev, BSC}$ = *A* x TCL *(mg)*	3X-1c / 12hrs aeration Results (mg)	3X-2c / 12hrs aeration Results (mg)	3X-3c / 12hrs aeration Results (mg)
EO	Not to exceed 10 µg/cm^2	3X, 12-hour heated aeration	99.9	0.999	0.2919	0.2987	0.2480
ECH	Not to exceed 5 mg/cm^2			499.5	N/D*	N/D*	N/D*

*N/D = Not detected

Per ISO 10993-7:2008, dissipation curves are used to estimate the post-sterilization time required for products to reach residue limits, principally for EO. Dissipation of EO from most materials and devices follows first-order kinetics. A plot of the natural logarithm of the experimentally determined EO concentration against time after sterilization is linear. Release shall then be based on the time after sterilization when the mean regression line intersects the maximum allowable residue.

Regression analysis of pooled data from three lots established the nature of the dissipation curve, enabling the model device to be released at the calculated upper 95% prediction limit for it., *L*p, for the allowed residue limit for the product.

The ISO 10993-7:2008 Residual Regression Equation is as follow:

$$L_p = x_o + t_\alpha \times \sqrt{\frac{(S_\alpha)^2}{b^2} \times \left[1 + \frac{1}{n} + \frac{(y_o - y_\mu)^2}{b^2 \times \sum (x_i - x_\mu)^2}\right]} \qquad x_o = \frac{y_o - a}{b}$$

where
*x*o is the calculated average value of the release time corresponding to the EO limit;
*y*o is the logarithmic value of the EO limit;
a is the intercept of the linear regression line obtained from the plot ln[EO]α time;
b is the slope of the regression line;
*L*p is the prediction limit for a single individual of the product;
*t*α is the student *t* value at significance α with *n* − 2 degrees of freedom;
(*S*α)2 is the residual variance of the regression line;
*y*μ is the average of logarithmic EO values;
n is the number of values;
*x*i is the individual time after sterilization at which measurements are made;
*x*μ is the average of the times after sterilization;
Σ (*x*i − *x*μ)2 is the sum of squares for *x* (time).

For Ascenda ADT kit, three sterilization cycles were performed for each sample point. A total of 18 units and 1 blank control samples were analyzed. The worst-case component are the identified as Exhaustive Contact Components Pooled in Table 16, since are the only one required to calculate TCL values.

Right after one hour of forced aeration, the Exhaustive Contact Components Pooled samples showed a highest initial concentration of 1.2441 mg/device of EO residual level for 1X sterilization and 1.5696 mg/device of EO residual level for 3X sterilization, which is lower than the established limits of 4mg/device.

Test results are documented in Tables 18 through Table 30. Based on these summarized results the EO, ECH and TCL residuals requirements are met as soon as 1 hour of forced aeration for 1X and 3X sterilization. Nevertheless, based on the 95% Prediction Limit calculation, included in Attachment #12 and #13, to reach the limits of EO that meet the TCL requirements, a total of 5:00hrs are required after 1X sterilization and 6:00hrs are required after 2X and 3X sterilization.

For pooled Limited exposure components (Trident Guidewire Assembly 26 in., ADT Base, ADT Handle, Needle Catheter Introducer 4.5 in.), EO and ECH residuals requirements are met as soon as 1 hour of forced aeration for 1X and 3X sterilization.

The residual levels of ECH for all samples did not exceed the maximum limits established since the first sample was analyzed. The ECH TCL was met at 1-hour aeration.

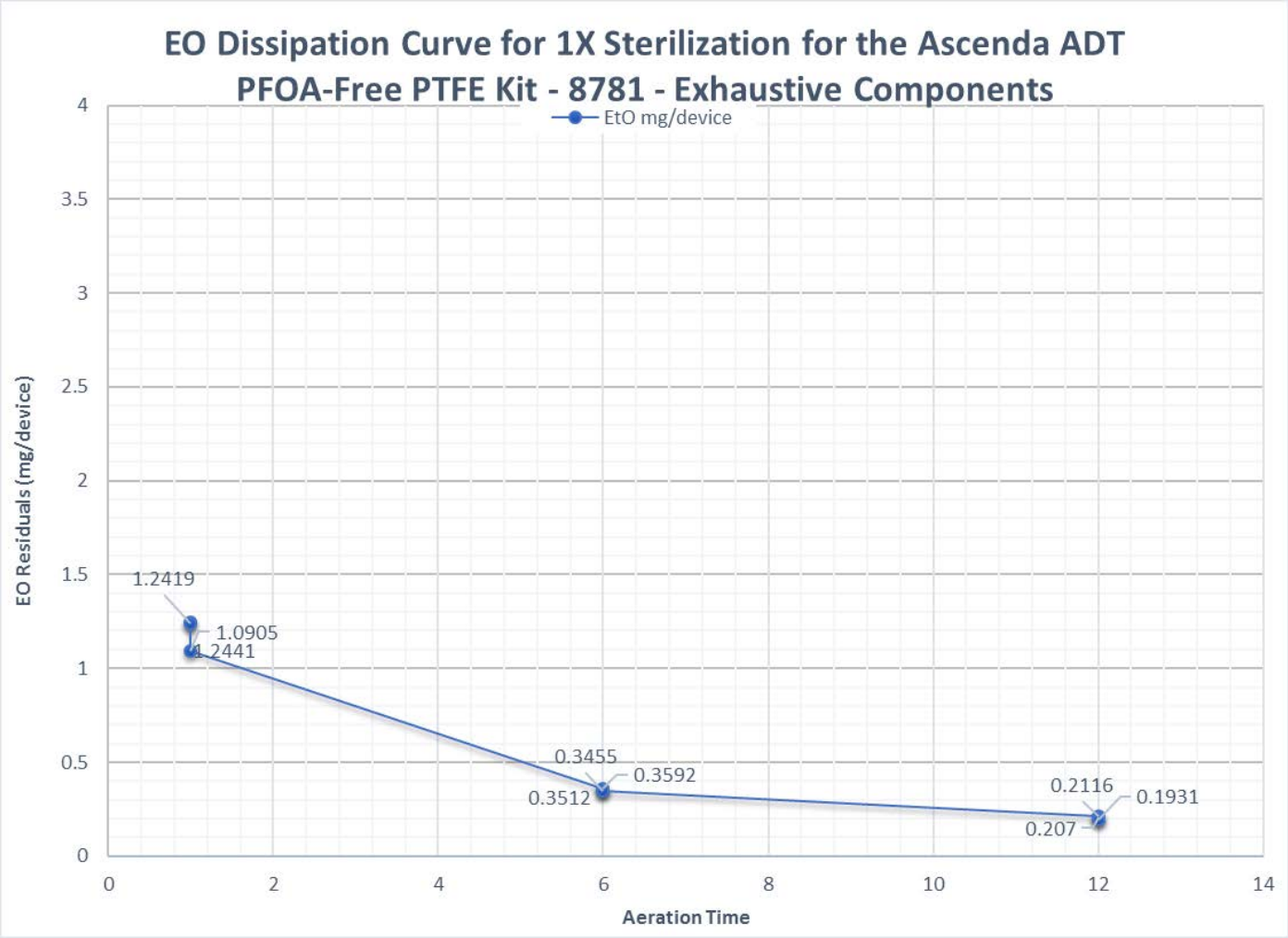

Figure 5. EO Dissipation Curve for 1X Sterilization for the Ascenda ADT PFOA-Free PTFE Kit - 8781 - Exhaustive Components

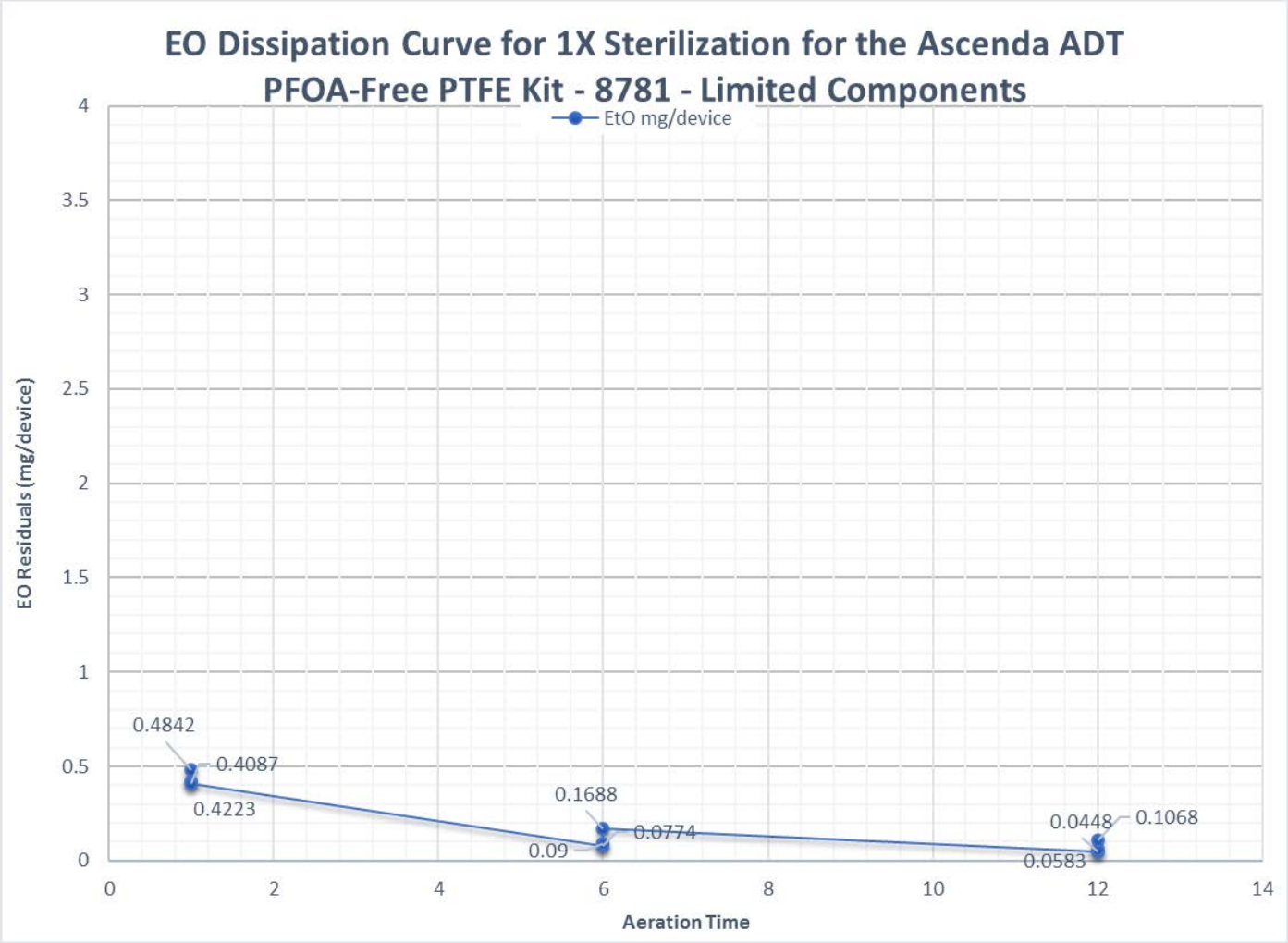

Figure 6. EO Dissipation Curve for 1X Sterilization for the Ascenda ADT PFOA-Free PTFE Kit - 8781 - Limited Components

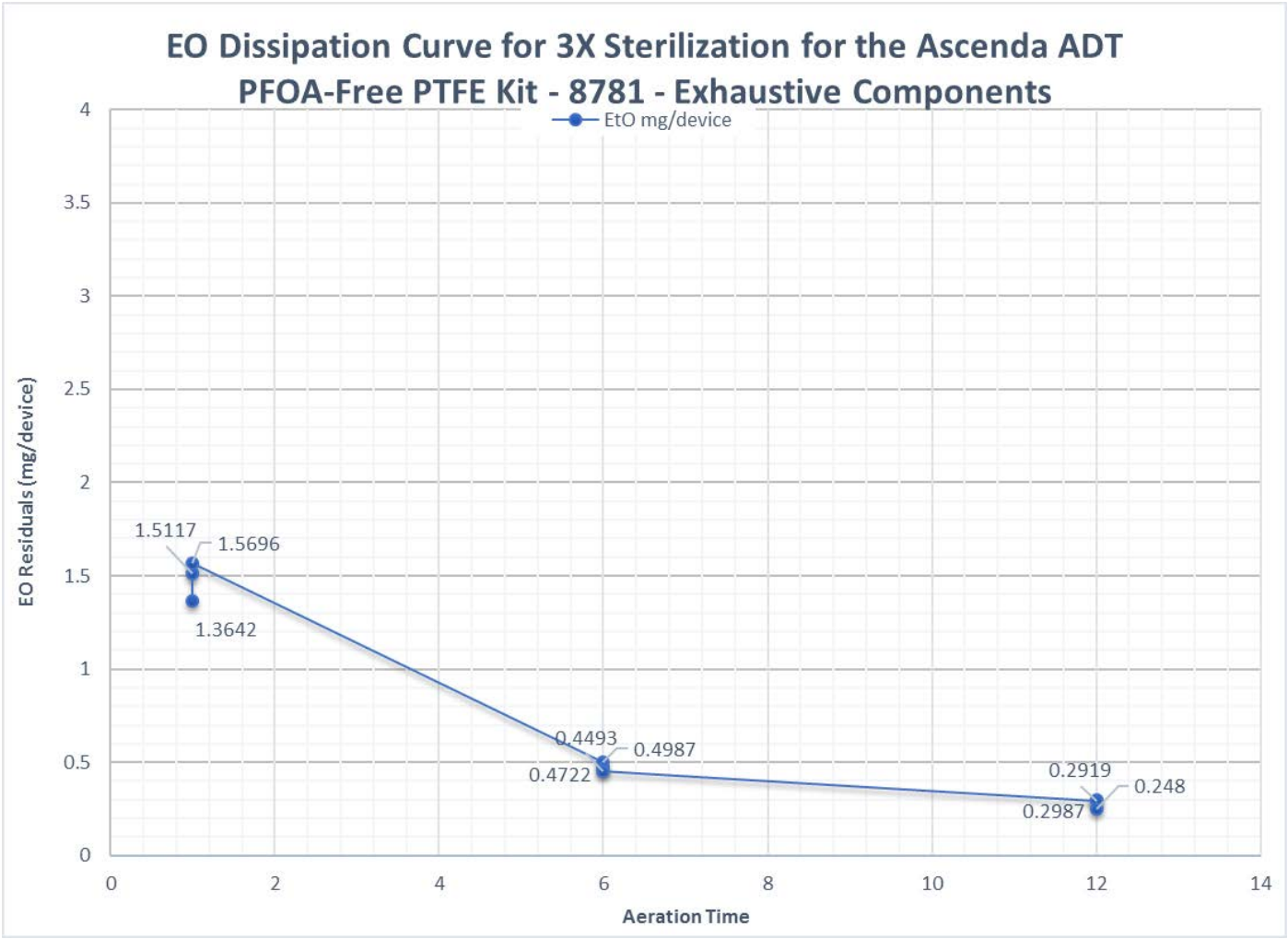

Figure 7. EO Dissipation Curve for 3X Sterilization for the Ascenda ADT PFOA-Free PTFE Kit - 8781 - Exhaustive Components

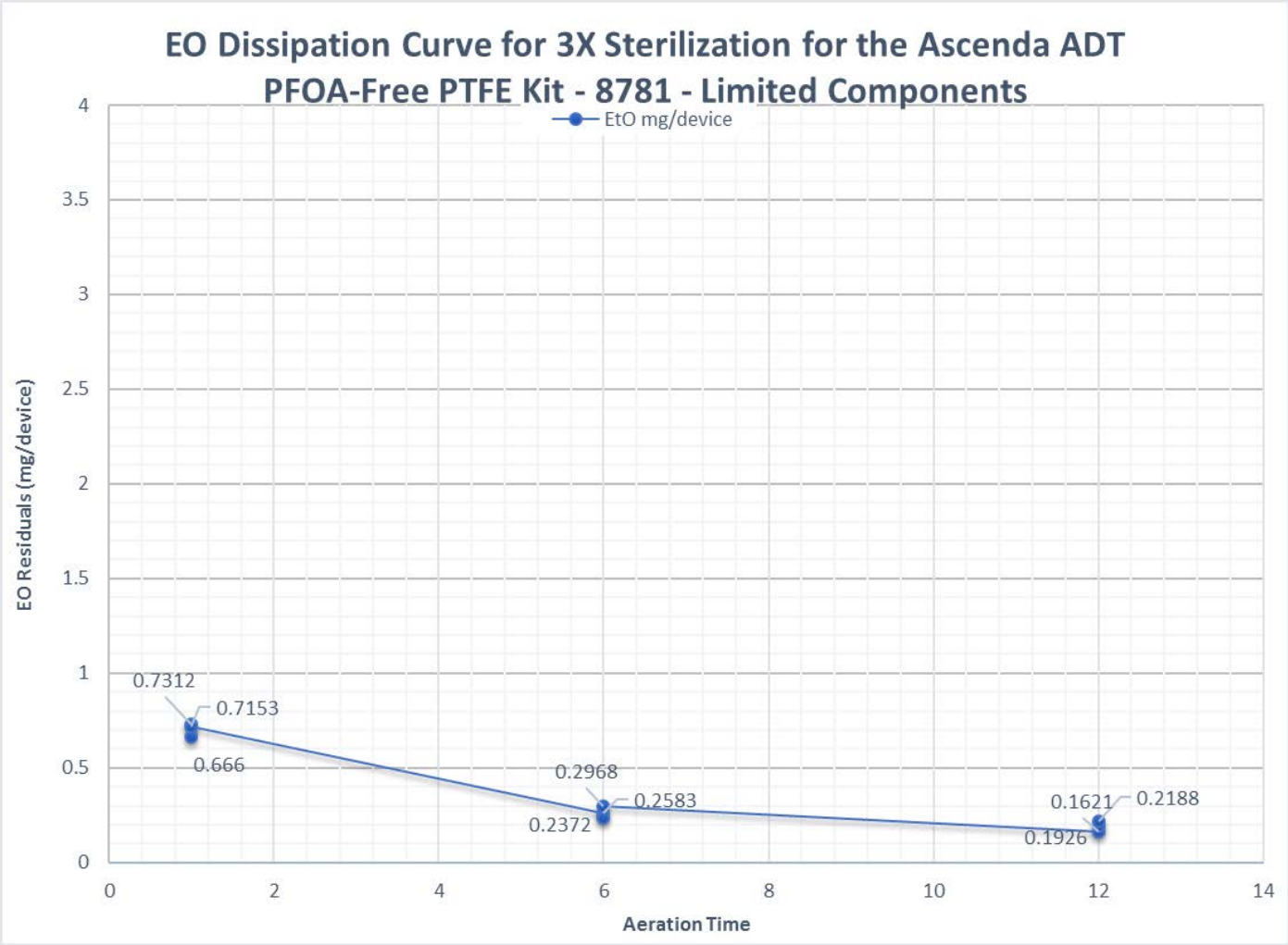

Figure 8. EO Dissipation Curve for 3X Sterilization for the Ascenda ADT PFOA-Free PTFE Kit - 8781 - Limited Components

8. Protocol Deviations

No deviation was created as part of the validation activities.

9. Re-qualification Requirements

An assessment will be conducted annually (per DOC000517) to determine if sterilant residual testing is required.

10. Conclusion

The minimum periods of forced heat aeration following sterilization exposure for the Ascenda ADT PFOA-Free PTFE Kit product model in the scope of this qualification are described below in Table 31. The maximum aeration allowed is 26 hours of forced heat aeration following each sterilization exposure.

Table 31 – Minimum Aeration Times

Model	1X Aeration (hours)	2X / 3X Aeration(hours)
8781	5	6

The actual Ascenda ADT with PFOA PTFE Kit product model have a minimum time of forced heat aeration following 1X and 2X/3X sterilization exposure of 8 hours for the first sterilization cycle, and 16 hours for subsequent sterilization cycles. Therefore. this study confirms product meets requirements with current minimum aeration time.

11. Attachments

11.1 Attachment #1 – Training Attendance Sheet

11.2 Attachment #2 – D00064617 Data and Chart (Residual Run 1)

11.3 Attachment #3 – D00064617-2 Data and Chart (Residual Run 2)

11.4 Attachment #4 – D00064617-3 Data and Chart (Residual Run 3)

11.5 Attachment #5 – D00064617-4 Data and Chart (Residual Run 4)

11.6 Attachment #6 – D00064617-5 Data and Chart (Residual Run 5)

11.7 Attachment #7 – EO and ECH Laboratory Data Package – 1X

11.8 Attachment #8 – EO and ECH Laboratory Data Package – 3X

11.9 Attachment #9 – EO and ECH Summary Sheets – 1X

11.10 Attachment #10 – EO and ECH Summary Sheets – 3X

11.11 Attachment #11 – Ethylene Oxide Residual Freezer Samples Logs

11.12 Attachment #12 – EO Residual Calculator – 1X

11.13 Attachment #13 – EO Residual Calculator – 3X

11.14 Attachment #14 – Rationale for Process Parameters Not Included in Validation Report

11.15 Attachment #15 – MDT30068705 Ethylene Oxide Residuals in Medical Devices Used for Adults, Children, and Neonates